CLAIMS

What is claimed is:

1. A method for identifying potential therapeutic agents, comprising:

(a) contacting a target cell with a candidate therapeutic phosphoryl or phosphoramidate prodrug that is a selective substrate for a target enzyme, under conditions that favor the incorporation of the agent into the intracellular compartment of the target cell;

(b) assaying the target cell for inhibition of cellular proliferation or cell killing.

2. The method of claim 1, wherein the prodrug is a phosphoramidate derivative of 2'-deoxyuridine.

3. A method for identifying potential therapeutic agents, comprising:

(a) contacting a target cell with a candidate therapeutic phosphoryl or phophoramidate prodrug having a detectably labeled toxic leaving group and that is a selective substrate for a target enzyme, under conditions that favor the incorporation of the agent into the intracellular compartment of the target cell;

(b) assaying the culture media for the amount of label released and comparing it to the amount of label released.

4. The method of claim 3, wherein the prodrug is a phosphoramidate derivative of 2'-deoxyuridine.

5. The method of claims 1 or 3, wherein the target cell is characterized as resistant to a chemotherapeutic drug.

6. The method of claims 1 or 3, wherein the target enzyme is amplified as a result of selection *in vivo* by chemotherapy.

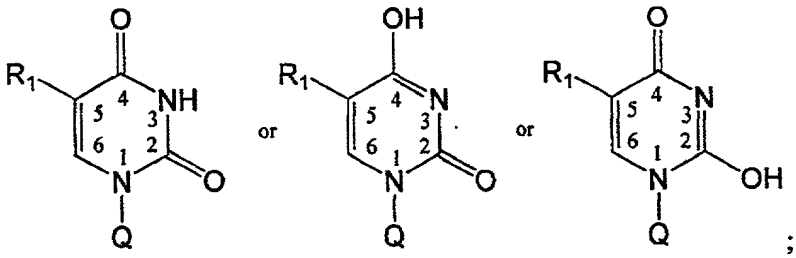
7. The method of claims 1or 3, wherein the target enzyme is an endogenous intracellular enzyme that is overexpressed in the target cell.

8. The method of claims 1 or 3, wherein the target enzyme is thymidylate synthase.

9. A method for inhibiting the proliferation of a hyperproliferative cell, comprising contacting the cell with a phosphoryl or phorphoramidate prodrug that is selectively converted to a toxin in the cell by an endogenous, intracellular enzyme.

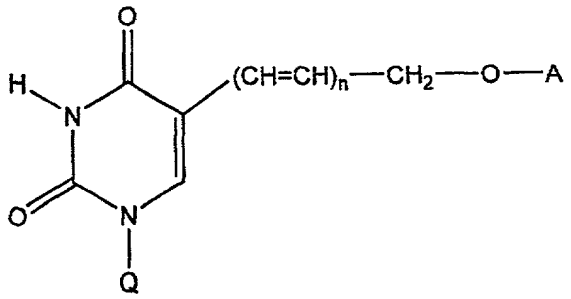
10. A method for treating a pathology characterized by hyperproliferative cells in a subject comprising administering to the subject a phosphoryl or phosphoramidate prodrug that is converted to a toxin in a hyperproliferative cell by an intracellular enzyme that is endogenously overexpressed or over-accumulated in the cell.

11. The method of any of claims 9 or 10, wherein the candidate therapeutic agent is an L- or D- compound of the formula:



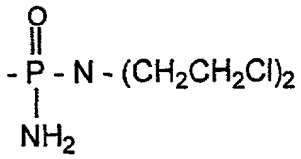
;

wherein R_1 is or contains a chemical entity that has a molecular dimension and electrophilicity compatible with extraction from the pyrimidine ring by thymidylate synthase, and which upon release from the pyrimidine ring by thymidylate synthase has the ability to inhibit the proliferation of the cell or kill the cell; or a compound of the formula:



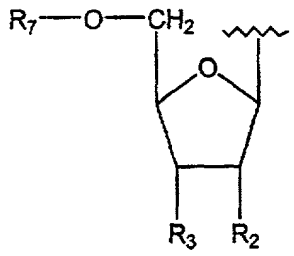
;

wherein n is an integer from 0 to 10; wherein A is a phosphoryl or phosphoramide derivative, or a compound of the formula:



wherein Q is a phosphoryl or phosphoramidate derivative containing a chemical entity selected from the group consisting of sugar groups, thio-sugar groups, carbocyclic groups, and derivatives thereof.

12. The method of claim 11, wherein Q has the formula:

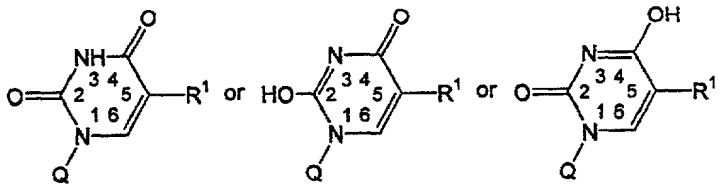


wherein R_7 is selected from the group consisting of phosphoryl, phosphoramidate and derivatives thereof, and wherein R_2 and R_3 are the same or different and are independently -H or -OH.

13. The method of claim 11, wherein R_1 is a halogen.

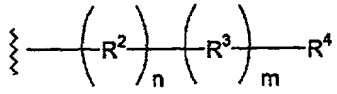
14. The method of claim 11, wherein R_1 is an alkyl group, i.e., $(-CH=CH)_n-R_4$, wherein n is an integer from 0 to 10, and R_4 is selected from the group consisting of H, a halogen, alkyl, alkene, alkyne, hydroxy, -O-alkyl, -O-aryl, O-heteroaryl, -S-alkyl, -S-aryl, -S-heteroaryl, $-NH_2$, -NH-alkyl, $-N(alkyl)_2$, -NHCHO, a cyanide, cyanate and thiocyanate cyanide, cyanate and thiocyanate halovinyl compound, a halomercuric compound, -NHOH, -NHO-alkyl, and $NHNH_2$.

15. A compound of the formula:



wherein:

R^1 is a moiety of the formula:



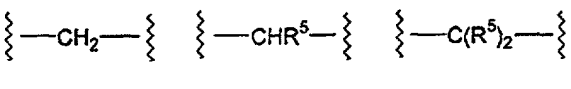
R^2 is a divalent electron conduit moiety selected from the group consisting of:

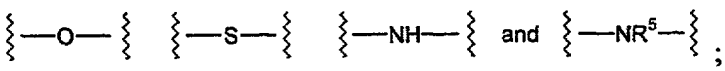
an unsaturated hydrocarbyl group;

an aromatic hydrocarbyl group comprising one or more unsaturated hydrocarbyl groups; and,

a heteroaromatic group comprising one or more unsaturated hydrocarbyl groups;

R^3 is a divalent spacer moiety selected from the group consisting of:



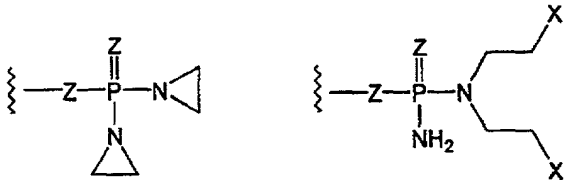


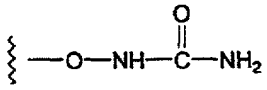
R^5 may be the same or different and is independently a linear or branched alkyl group having from 1 to 10 carbon atoms, or a cycloalkyl group having from 3 to 10 carbon atoms;

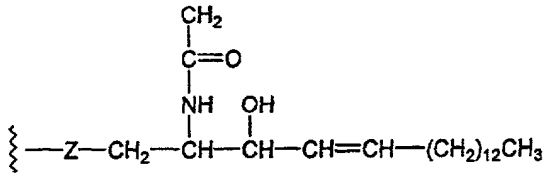
n is an integer from 0 to 10;

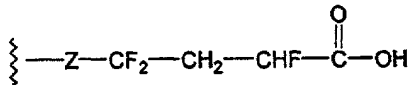
m is 0 or 1;

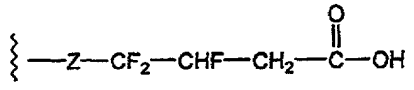
R^4 is a toxophore moiety selected from the group consisting of:

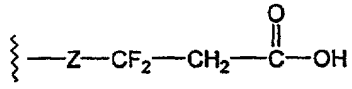


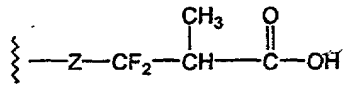


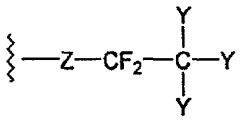


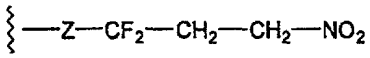




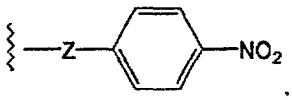








and

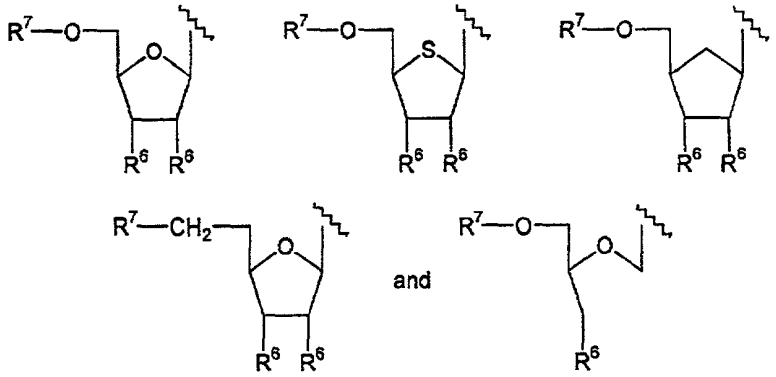


X is -Cl, -Br, -I, or other potent leaving group, with the proviso that when R^7 is -H, and M is zero, then R^4 is not a halogen or when m is zero and n is zero, then R^4 is not a halogen;

Y is independently -H or -F;

Z is independently -O- or -S-;

Q is a sugar moiety selected from the group consisting of:

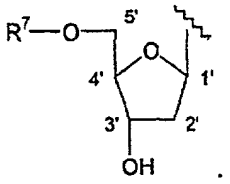


R^6 is independently -H, -OH, $-OC(=O)CH_3$, or other protected hydroxyl group; and,

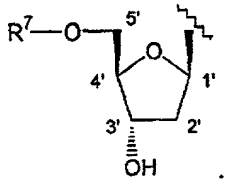
R^7 is hydrogen, a phosphate group, or a phosphoramidate group;

and wherein said compound may be in any enantiomeric, diasteriomeric, or stereoisomeric form, including, D-form, L-form, α-anomeric form, and β-anomeric form.

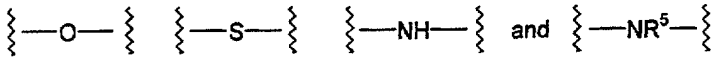
16. A compound according to claim 15, wherein Q is:



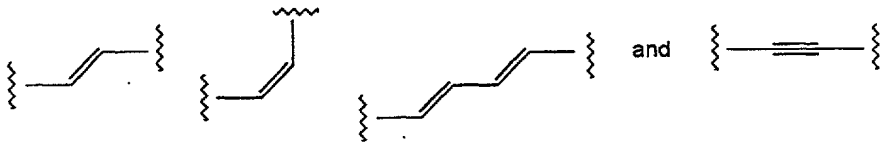
17. A compound according to claim 15, wherein Q is:



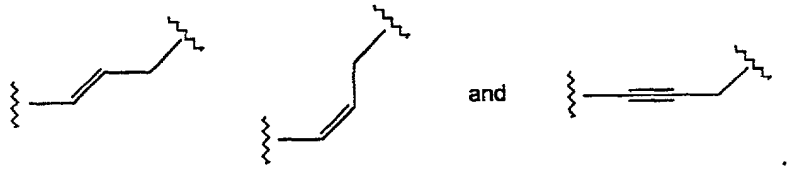
18. A compound of claim 15, wherein R^3 is a divalent spacer moiety selected from the group consisting of:



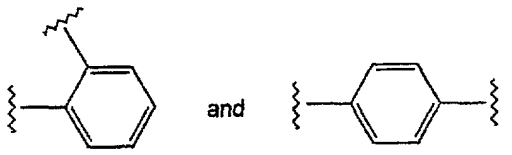
19. A compound of claims 15, wherein R^2 is an unsaturated hydrocarbyl group selected from the group consisting of:



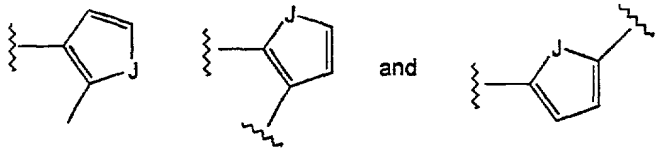
20. A compound of claim 15, wherein R^2 and R^3, taken together form a structure selected from the group consisting of:



21. A compound of claim 15, wherein R^2 is an aromatic hydrocarbyl group selected from the group consisting of:

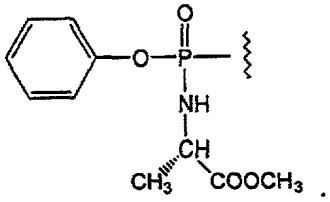


22. A compound of claim 15, wherein R^2 is a heteroaromatic group selected from the group consisting of:

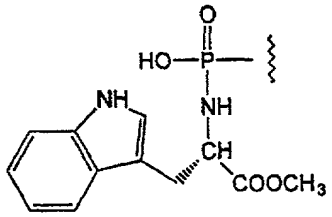


wherein J is -O-, -S-, -Se-, -NH-, or $-NR^{ALK}-$, wherein R^{ALK} is a linear or branched alkyl having 1 to 10 carbon atoms or a cycloalkyl group having 3 to 10 carbon atoms.

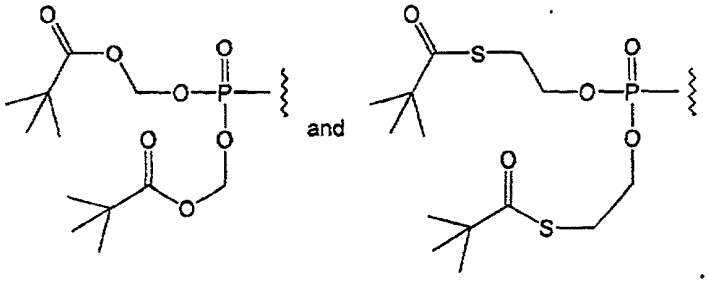
23. A compound of claims 15, wherein R^7 is selected from the group consisting of:



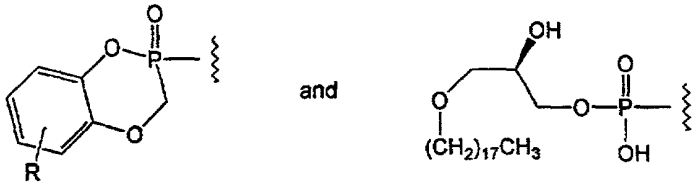
24. A compound of claim 15, wherein R^7 is selected from the group consisting of:



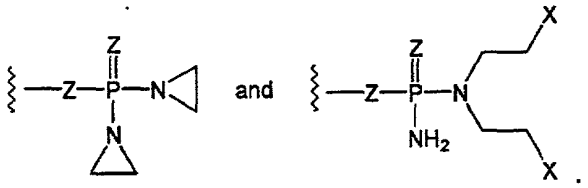
25. A compound of claim15, wherein R^7 is selected from the group consisting of:



26. A compound of claim 15, wherein R^7 is selected from the group consisting of:

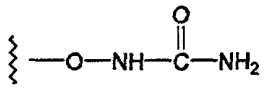


27. A compound of claim 15, wherein R^4 is selected from the group consisting of:

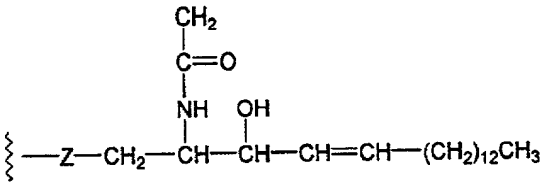


28. A compound of claim 15, wherein R^4 is selected from the group consisting of:

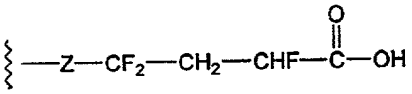
29. A compound of claim 15, wherein R^4 is:

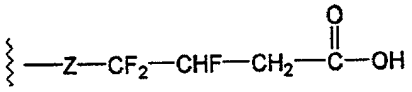


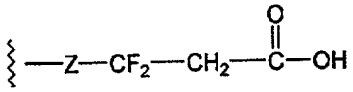
30. A compound of claim 15, wherein R^4 is:

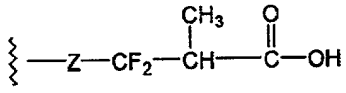


31. A compound of claim 15, wherein R^4 is:

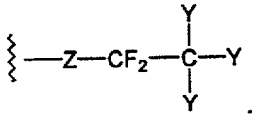




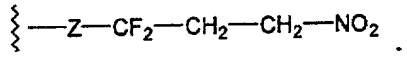

or



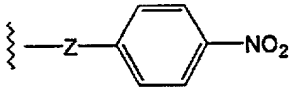
32. A compound of claim 15, wherein R^4 is:



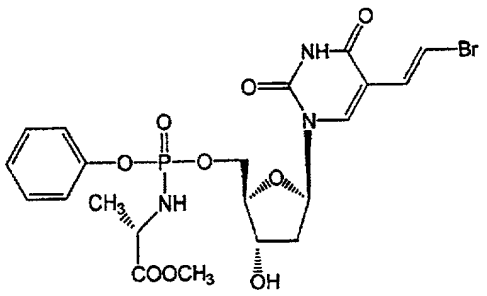
33. A compound of claim 15, wherein R^4 is:



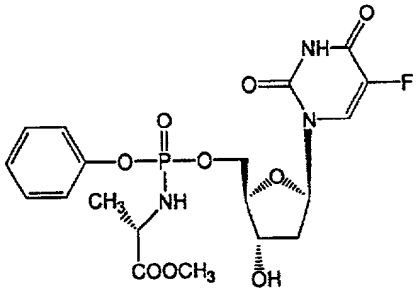
34. A compound of claim 15, wherein R^4 is:



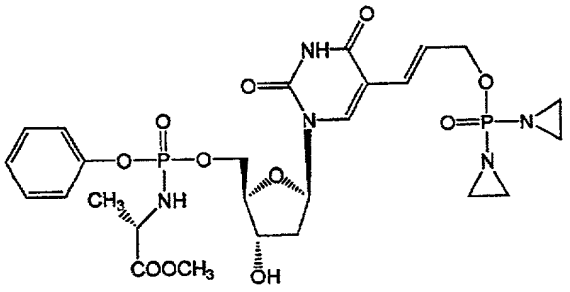
35. A compound of the formula:



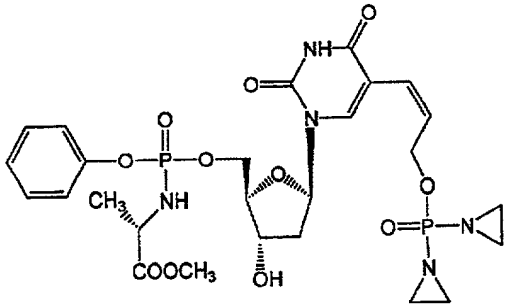
36. A compound of the formula:



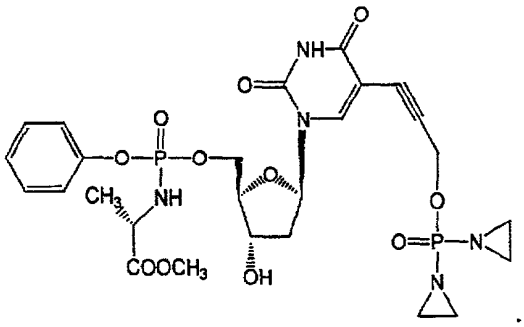
37. A compound of the formula:



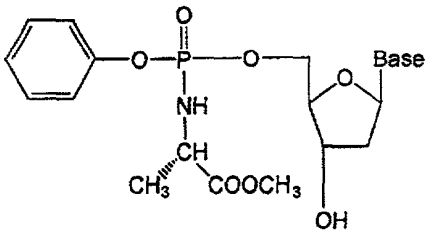
38. A compound of the formula:



39. A compound of the formula:

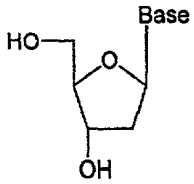


40. A method of forming a compound of the formula:

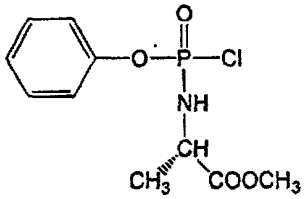


wherein "Base" denotes a nucleic acid base;

which method comprises the step of reacting a compound of the formula:

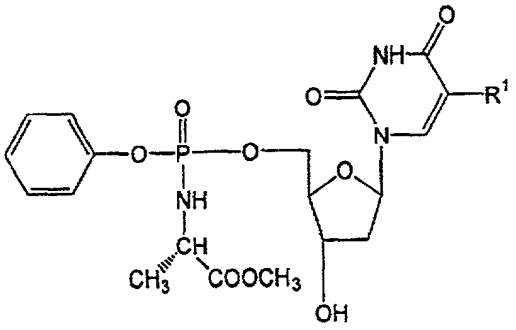


with a compound of the formula:



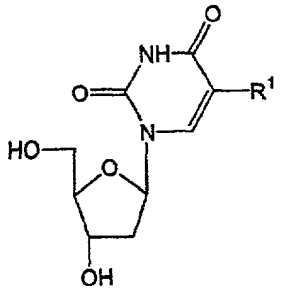
in the presence of an HCl scavenger.

41. A method of forming a compound of the formula:

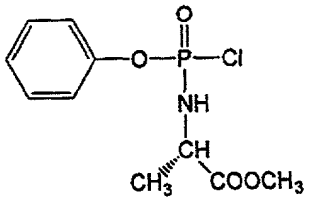


wherein R^1 is a substituent;

which method comprises the step of reacting a compound of the formula:



with a compound of the formula:



in the presence of an HCl scavenger.

42. The method according to claim 40 or 41, wherein said HCl scavenger is imidazole.

43. The method according to any one of claims 40 to 42, wherein said reaction is performed in a non-aqueous solvent comprising dimethylformamide.

44. A method for screening for a therapeutic agent, comprising:

(a) contacting a first target cell with a compound of any of claims 15 or 37 to 39, under conditions that favor the incorporation of the compound into the intracellular

compartment of the target cell and a second target cell with a potential therapeutic agent, under conditions that favor the incorporation of the compound into the intracellular compartment of the target cell; and

(b) assaying the second target cell for inhibition of cellular proliferation or cell killing.

45. The method of claim 44, wherein the target cell is characterized as resistant to a chemotherapeutic drug.

46. The method of claim 44, wherein the target cell is characterized as expressing a target enzyme that is amplified as a result of selection *in vivo* by chemotherapy.

47. The method of claim 46, wherein the target enzyme is an endogenous intracellular enzyme that is overexpressed in the target cell.

48. The method of claim 47, wherein the endogeneous overexpression of an intracellular enzyme is the result of amplification of the gene coding for the enzyme.

49. The method of claim 47, wherein the enzyme is thymidylate synthase.

50. Use of a compound of any of any of claims 15 or 37 to 39, for the preparation of a medicament to treat inhibit the proliferation of a cell.

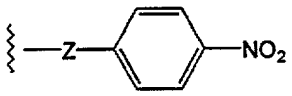
51. A method for inhibiting the proliferation of a hyperproliferative cell, comprising contacting the cell with an effective amount of a compound of any of claims 15 or 37 to 39.

52. The method of claim 51, wherein the hyperproliferative cell is characterized by the endogenous overexpression of an intracellular enzyme.

53. The method of claim 52, wherein the enzyme is thymidylate synthase.

54. A method for treating a pathology characterized by hyperproliferative cells in a subject comprising administering to the subject a compound of any of claims 15 or 37 to 39.

55. A method for screening for a therapeutic agent, comprising contacting a target cell with a compound of any of claims 15 or 37 to 39, wherein R^4 is:



which target cell favor the incorporation of the compound into the target cell, for the diagnostic purpose of detecting intracellular levels of thymidylate synthase.